Chimeric liver transplantation reveals interspecific graft remodelling.

Journal: J Hepatol

Publication Year: 2018

Authors: Graziano Oldani, Andrea Peloso, Sandrine Vijgen, Elizabeth M Wilson, Florence Slits, Quentin Gex, Philippe Morel, Vaihere Delaune, Lorenzo A Orci, Tomoyuki Yamaguchi, Toshihiro Kobayashi, Laura Rubbia-Brandt, Hiromitsu Nakauchi, Stephanie Lacotte, Christian Toso

PubMed link: 30031887

Funding Grants: Generation of functional cells and organs from iPSCs

Public Summary:
Chimeric animals are composed of cells from different species. Chimeric animals carrying human tissue have the potential to increase the availability of transplantable organs. We transplanted rat-to-mouse liver grafts into newly weaned rats. The chimeric grafts underwent post-transplant remodelling with rat hepatocytes replacing all mouse hepatocytes within 56 days. In addition, we observed the post-transplant development of diffuse mature rat bile ducts through the transformation of hepatocytes, and patchy areas of portal endothelium originating from the host. These data demonstrate the efficacy of transplanting rat-to-mouse chimeric livers into rats, with a high potential for post-transplant graft remodelling.

Scientific Abstract:
BACKGROUND & AIMS: A major limitation in the field of liver transplantation is the shortage of transplantable organs. Chimeric animals carrying human tissue have the potential to solve this problem. However, currently available chimeric organs retain a high level of xenogeneic cells, and the transplantation of impure organs needs to be tested. METHODS: We created chimeric livers by injecting Lewis rat hepatocytes into C57Bl/6(Fah)(-/-)(Rag2)(-/-)(Il2rg)(-/-) mice, and further transplanted them into newly weaned Lewis rats (45+/-3g) with or without suboptimal immunosuppression (tacrolimus 0.6mg/kg/day for 56 or 112days). Control donors included wild-type C57Bl/6 mice (xenogeneic) and Lewis rats (syngeneic). RESULTS: Without immunosuppression, recipients of chimeric livers experienced acute rejection, and died within 8 to 11days. With immunosuppression, they all survived for >112days with normal weight gain compared to syngeneic controls, while all xenogeneic controls died within 98days due to rejection with Banff scores >6 ($p=0.0014$). The chimeric grafts underwent post-transplant remodelling, growing by 670% on average. Rat hepatocytes fully replaced mouse hepatocytes starting from day 56 (absence of detectable mouse serum albumin, histological clearance of mouse hepatocytes). In addition, rat albumin levels reached those of syngeneic recipients. Four months after transplantation of chimeric livers, we observed the development of diffuse mature rat bile ducts through transdifferentiation of hepatocytes (up to 72% of cholangiocytes), and patchy areas of portal endothelium originating from the host (seen in one out of five recipients). CONCLUSIONS: Taken together, these data demonstrate the efficacy of transplanting rat-to-mouse chimeric livers into rats, with a high potential for post-transplant recipient-oriented graft remodelling. Validation in a large animal model is still needed. LAY SUMMARY: Chimeric animals are composed of cells from different species. Chimeric animals carrying human tissue have the potential to increase the availability of transplantable organs. We transplanted rat-to-mouse liver grafts into newly weaned rats. The chimeric grafts underwent post-transplant remodelling with rat hepatocytes replacing all mouse hepatocytes within 56days. In addition, we observed the post-transplant development of diffuse mature rat bile ducts through the transformation of hepatocytes, and patchy areas of portal endothelium originating from the host. These data demonstrate the efficacy of transplanting rat-to-mouse chimeric livers into rats, with a high potential for post-transplant graft remodelling.